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Help

Logout

Interrupt

Main Menu

Search Form

Posting Counts

Show S Numbers

Edit S Numbers

Preferences

Search Results -

Terms	Documents
l4 and switch	4

Database:

US Patents Full-Text Database

JPO Abstracts Database

EPO Abstracts Database

Derwent World Patents Index

IBM Technical Disclosure Bulletins

Refine Search:

l4 and switch

Clear

Search History

Today's Date: 10/5/2000

<u>DB Name</u>	<u>Query</u>	<u>Hit Count</u>	<u>Set Name</u>
USPT	l4 and switch	4	<u>L5</u>
USPT	l2 and l3	61	<u>L4</u>
USPT	l1 and device	9915	<u>L3</u>
USPT	l1 and antigen	141	<u>L2</u>
USPT	lock near4 key	14065	<u>L1</u>

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Generate Collection

Search Results - Record(s) 1 through 4 of 4 returned.☐ 1. Document ID: US 5411550 A

L5: Entry 1 of 4

File: USPT

May 2, 1995

DOCUMENT-IDENTIFIER: US 5411550 A

TITLE: Implantable prosthetic device for the delivery of a bioactive material

ABPL:

An implantable prosthetic device for sustained release of a bioactive material into a fluid flow pathway of a patient comprises a body adapted for attachment to the fluid flow pathway. The body defines a primary lumen for accommodating fluid flow therethrough and at least one secondary lumen at least a portion of which is separated from the primary lumen by a wall sufficiently permeable to permit a bioactive material disposed in the lumen to diffuse through the wall and into the primary lumen. The bioactive material can be either a therapeutic or diagnostic agent. In a particular embodiment of the invention, the device comprises a tubular body consisting of stretched and/or expanded polytetrafluoroethylene and is adapted for attachment to a blood vessel of a patient.

BSPR:

One type of implantable device is a synthetic vascular graft such as is commonly used to replace damaged or dysfunctional arterial or venous pathways, for example at the site of an aneurysm or occlusion. Bypass grafts are often used to divert blood flow around damaged regions to restore blood flow. Another use of vascular prostheses is for creating a bypass shunt between an artery and vein, specifically for multiple needle access, such as is required for hemodialysis treatments. Following multiple percutaneous invasions into a vein, the vein may either collapse along the puncture track or become aneurysmal, leaky or fill with clot, causing significant risk of pulmonary embolization. Vascular prostheses have been used for many years as an alternative to patients' own veins for vascular access during hemodialysis.

BSPR:

In an effort to address these problems, various types of vascular access devices have been developed. One example of such a device is described by Tesio in U.S. Pat. No. 4,898,669 (Feb. 6, 1990). This device is a catheter system mechanically coupled with a prosthetic vascular graft for use in blood purification. Devices available for long-term, repeated vascular access allow a catheter to be introduced to a blood flow pathway, but they do not generally allow chronic, permanent implantation. In some cases, due to the materials used, an autoimmune response occurs resulting in the formation of an occlusive hematoma.

BSPR:

Another vascular graft is disclosed in U.S. Pat. No. 4,619,641 (Oct. 28, 1986) to Shanzer which discloses a coaxial double lumen device for use in hemoaccess. The space between the two lumina is filled with a self-sealing, non-biodegradable polymer which does not permit escaped bleeding following needle puncture. The Shanzer product consists of an outer tube positioned over an inner tube, both tubes being made of expanded PTFE.

BSPR:

Additionally, recently published evidence indicating that cellular activities are controlled by receptors, "molecular switches" on the membrane surface of cells suggests that bioactive and pharmaceutical drug interactions, whether initiators or inhibitors, can be utilized to improve implantable organ and autogenous organ transplant performance. These receptors control cellular activities by binding

with highly specific substances referred to as "ligands." Like the action of a key in a lock, ligands fit into receptors and, if the fit is precise, turn on or off certain cellular processes. Some ligands act as antagonists to inhibit cellular activities by blocking a receptor. Research has shown that many aspects of cardiovascular disease are controlled by specific cell surface receptors.

BSPR:

The invention features an implantable, biocompatible prosthetic device for the sustained release of a drug or other bioactive material directly into a blood or other body fluid flow path. The device is a polymeric bi- or multilumenal tubular article which can be attached, for example, to an artery or vein to form a vascular graft or shunt. The device can also be used to provide organ to organ fluid communication. The device contains a primary lumen, which is dedicated to the flow of blood or other body fluid and at least one secondary lumen. The lumina are separated by a microporous, semi-permeable wall which permits passage of an agent from the secondary lumen to the primary lumen. Additionally, the microporosity of the separating wall promotes the growth, motility, and/or migration of cells into and through the wall.

BSPR:

In one embodiment of the invention, the prosthetic device comprises a tube which is adapted for attachment to a blood flow pathway, and for conducting the flow of blood therethrough. The tube has a biocompatible or bioinert exterior surface, and defines a primary lumen axially extending along the length of the tube, and at least one additional or secondary lumen. The secondary lumen is separated from the first lumen by a microporous wall which allows a drug introduced into the secondary lumen to diffuse across the wall and into the primary lumen, and thus directly into the blood flow pathway. This is caused by patient cells penetrating the exterior wall of the tube and displacing air contained in the micropores of the tube's microporous structure. The displaced air, in turn, displaces material contained in the secondary lumen forcing the material to diffuse into the primary lumen.

BSPR:

In another embodiment of the invention, the tube features an external drug delivery device attached thereto by a second tube or catheter. The catheter is connected to the secondary lumen. The delivery device injects the drug into the secondary lumen from an external source. The device can be any of a variety of commercially and technologically available systems, such as, for example, a biologically activated mini-pump which is either subcutaneously or extracutaneously located, or an external mechanical pump.

BSPR:

The present prosthetic device is preferably made from stretched and expanded polytetrafluoroethylene (PTFE). Stretched and expanded PTFE contains a porous network of nodes and fibrils which are created during the stretching and expansion process of porous tubing from PTFE. This porous network provides a semi-permeable wall or membrane between the lumina of the device.

BSPR:

In another aspect, the invention features a method for delivering directly into a fluid flow pathway in a controlled manner a bioactive material, such as a prophylactic or therapeutic drug, or a diagnostic material, such as a radiolabeled antibody. One embodiment of this aspect of the invention includes the steps of pre-filling one of the secondary lumina of the above-described implantable device with a bioactive material and implanting the device in a fluid flow pathway such as a vein or artery. In this manner, fluid flow is established through the primary lumen of the device. The pre-filled material diffuses across the wall or membrane separating the secondary lumina from the primary lumen in a controlled manner, thereby delivering the drug directly into the fluid, blood or otherwise, flowing through the primary lumen.

BSPR:

The invention has several advantages. It allows implantable vascular grafting and controlled and/or continuous drug delivery to be combined. Additionally, the invention allows a bioactive substance to be delivered directly into a patient's bloodstream at a controlled rate without using intravenous injection, which generally must be performed in a hospital or doctor's office. The device and method allow a bioactive substance to be injected into the secondary lumen all at

once from an external source, then released into the patient's bloodstream at a slower, continuous rate as the substance passes from the secondary lumen into the primary lumen of the graft. This sustained release of a substance into the bloodstream over time is less likely than known drug delivery methods to result in distal embolization. The graft provides a site for repeated cannulation which does not require directly accessing the bloodstream and therefore reduces the incidence of bleeding at the injection site.

DRPR:

FIG. 1C, 1D and 1E show schematic cross-sectional views of alternative configurations of the biluminal device of FIG. 1A.

DRPR:

FIG. 2 shows a schematic front elevation view of a die used in the manufacture of the biluminal device of FIG. 1A.

DRPR:

FIG. 3 is a schematic side elevation view of a biluminal device in which the secondary lumen is partially co-extensive with the primary lumen.

DRPR:

FIG. 4 is a schematic perspective view of a multiluminal device of the invention.

DEPR:

In its broadest aspect, the invention features a multi-luminal prosthetic device for implantation into a patient. The invention can be utilized, for example, as a vascular graft providing sustained release of a selected bioactive agent or diagnostic material directly into a blood or other fluid flow pathway. The device has at least two lumina which are separated by a porous, semi-permeable wall. In the case of the device being used as a vascular graft, it is grafted onto a vein or artery in an individual such that the primary lumen becomes part of the individual's blood flow pathway. The secondary lumen is filled with a material such as, for example, a bioactive or diagnostic agent and the porous wall between the lumina allows the material disposed in the secondary lumen to diffuse into the bloodstream flowing through the primary lumen. As described in further detail below, the device allows the release of the material across the wall or membrane into the bloodflow pathway in a controlled manner.

DEPR:

The device comprises a main, or primary lumen, which is of a diameter sufficient to allow blood flow appropriate for the artery or vein to which it is attached to occur. Thus, the device has the geometric configuration of a tube, open at least at one end, and typically at both ends. The open end is sutured to an opening in the patient's arteriovenous pathway, thus becoming an extension of that pathway.

DEPR:

The device also contains at least one secondary lumen adjacent to the first lumen. At least one of the secondary lumina contains or is adapted to contain the selected bioactive or diagnostic materials. These materials can include, for example, therapeutic or prophylactic agents, such as a drug, protein, enzyme, antibody or other agent, or cells which produce a drug, protein, enzyme, antibody, or other agent. The diagnostic material can include, for example, a radiolabeled antibody or antigen.

DEPR:

Specific embodiments of the device are illustrated by the Figures. FIG. 1A shows a biluminal tubular structure 10 having a first lumen 12 and a secondary lumen 12'. The first lumen 12 has a structure sufficient for blood flow therethrough. For a vascular graft, the diameter of this lumen 12 is generally the same or similar in size to the host artery or vein to which it is grafted. As mentioned, however, the structure 10 can be formed to accommodate other types of fluid flow.

DEPR:

As shown in FIG. 1B, the secondary lumen 12' is adjacent the first lumen 12, and is separated by a semi-permeable, micro-porous, wall 14. The wall 14 has a permeability sufficient to allow diffusion of the bioactive agents or diagnostic material of choice from the secondary lumen 12' into the fluid flow pathway

defined by the first lumen 12. In a multi-lumen arrangement, i.e., a device having more than two lumina, the adjoining wall 14 lies in communication between each of the secondary lumina and the primary lumen. Alternatively, there can be a semi-permeable wall between each secondary lumen 12' and the first lumen 12, with an impermeable wall among the secondary lumina.

DEPR:

In another aspect, the invention features a method for delivering a bioactive agent or diagnostic material directly to a patient's body fluid, bloodstream or otherwise, in a controlled manner. In the method, a surgeon or other qualified person, surgically exposes the desired region of the patient for introduction of the prosthetic device 10. The desired site may, for example, be an area of occlusion or weakness in the patient's arteriovascular system. In such a case, during interruption of the patient's blood flow the prosthesis 10 is surgically implanted and sutured or otherwise secured in place. Proper positioning of the prosthesis 10 requires alignment of the primary lumen 12 with the blood flow pathway such that the blood flow is diverted through the primary lumen 12. The secondary lumen 12' either contains or is filled with a drug or agent of choice. The drug or agent perfuses across the interluminal wall 14 into the bloodstream at a controlled and substantially continuous rate. In this manner, the present invention allows continuous administration of the drug over a prolonged period of time similarly to controlled release systems which deliver a drug at a predetermined rate over a definite period of time.

DEPR:

In an example of use of the present invention, an antibody which is specific to a protein indicative of the presence of malignancy is introduced into the vascular system of a patient utilizing the present device and method. The device 10 is surgically implanted in a patient's vascular system and blood flow is established through the primary lumen 12. The antibody is added to the secondary lumen 12' either before implantation by pre-filling the lumen or after implantation by injecting the antibody composition into the secondary lumen. The antibody is labelled, for example, with a remotely detectable radioisotope such as 125.sub.I. The labelled antibody moves across the porous wall 14 between the primary lumen 12 and the secondary lumina 12' into the patient's blood flow pathway, which flows through the primary lumen 12. Once in the pathway, the labelled antibodies travel to the site of the malignancy and bind at the appropriate protein binding sites. The concentration of the radioisotope at the target site can then be detected using an appropriate detection device, e.g., a gamma camera. Additional doses of the antibody composition can be injected into the secondary lumen 12' through a cannula, or through a pre-attached catheter which communicates with the secondary lumen 12', without directly invading the patient's bloodstream.

DEPR:

The device 10 eliminates such needle and catheter injury to the blood vessel and large bolus chemical exposure to the native vessel with these highly toxic chemotherapy agents. Moreover, the device 10 can be replaced if long term therapy causes eventual failure or thrombus occlusion. A vein or artery permanently destroyed by chronic therapy, on the other hand, is irreplaceable. Similar problems and corresponding solutions also exist for hemodialysis patients whose native veins are consumed by repetitive needle penetration and permanent blood vessel wall injury.

DEPR:

After the PTFE resin is formed, such as by extrusion as discussed above, it is stretched and/or expanded and then sintered while being held in the stretched and/or expanded state. Stretching refers to elongation of formed resin while expansion refers to enlargement of the formed resin perpendicularly to its longitudinal axis. The rate of stretching and the stretch ratio affect the porosity of the finished product in a predictable manner allowing a prosthetic device to be produced having a specified porosity. The rate of stretching refers to the percentage of elongation per second that the resin is stretched while the stretch ratio refers to the relationship between the final length of the stretched resin and the initial length of the stretched resin. For example, stretching an extruded PTFE tube at a stretch ratio of two to one and a stretch rate of sixty results in a porosity of approximately forty. This porosity is unitless and is determined as set forth on page eighty-four of the American Society For Testing of Materials' Special Technical Publication Number 898. So, for example, based on stretch ratios ranging from two to one, to six to one, a

stretch rate of sixty percent per second yields a porosity of between approximately forty and approximately ninety, a stretch rate of one hundred and forty percent per second yields a porosity of between approximately sixty and approximately eighty-five, and a stretch rate of nine hundred percent per second yields a porosity of between approximately sixty-five and approximately eighty-five.

DEPR:

In addition to the porosity, the geometry of the node and fibril network of PTFE can be controlled during stretching and expansion. In the case of uniaxial stretching, that is, elongation of the formed PTFE resin along the direction of extrusion, the nodes are elongated causing the longer axis of each node to be oriented perpendicularly to the direction of stretch. Accordingly, the fibrils are oriented parallel to the direction of stretch. Axial stretching, additionally includes expanding the PTFE resin in the radial direction and can be utilized to produce a prosthetic device having a composite porosity. As in uniaxial stretching, the rate and ratio of radial expansion affects the resulting porosity of the prosthetic device.

DEPR:

The embodiment shown in FIG. 3 may be manufactured in a manner similar to that described above. The extrusion die for forming the partially-extending lumen may be modified in a manner known to those skilled in the art. For example, the die used in the extrusion of this embodiment of the invention may include a gate-type device which enables selective opening and closing of an aperture to coextrude a secondary lumen.

DEPR:

As shown in FIG. 5, the mini-pump 20 contains a drug reservoir 26 from which a connector tube 24 extends. The connector tube 24 may either be integral with the reservoir 26, or mechanically, detachably connected to the reservoir 26. The connector tube 24 extends from the reservoir 26 to a secondary lumen 12' of a prosthesis 10. The connector tube 24 may connect to the secondary lumen 12' by means of a mechanical attachment device 22, as illustrated, or may be formed integral with the secondary lumen 12'. Mechanical attachment devices are well known in the art, and include luer-locks. It is generally preferable that the mechanical attachment device is such that the mini-pump may readily be replaceable, thus attachment devices which do not require the application of pressure are preferable over pressure-lock devices.

CLPR:

1. An implantable prosthetic device for sustained release of a bioactive material into a fluid flow pathway of a patient comprising a single tubular body extruded as a continuous wall, said wall having at least two interior lumina formed therein, said body being adapted for attachment to said fluid flow pathway, and said continuous wall defining

CLPR:

2. A device as set forth in claim 1 wherein said bioactive material is a therapeutic agent.

CLPR:

3. A device as set forth in claim 1 wherein said bioactive material is a diagnostic agent.

CLPR:

4. A device as set forth in claim 1 wherein said device is a vascular graft having said primary lumen disposed to form a blood flow pathway.

CLPR:

5. A device as set forth in claim 1 wherein said device is an organ graft having said primary lumen disposed to form an organ to organ fluid flow pathway.

CLPR:

6. The device of claim 1 wherein said body consists of polytetrafluoroethylene (PTFE).

CLPR:

7. The device of claim 6 wherein said polytetrafluoroethylene is selected from

the group consisting of, expanded polytetrafluoroethylene, stretched polytetrafluoroethylene, and stretched and expanded polytetrafluoroethylene.

CLPR:

8. The device of claim 1 wherein said body consists of a material including copolymers.

CLPR:

9. An implantable prosthetic device for delivering a bioactive material into a blood vessel of a patient, the device comprising

CLPR:

10. A device as set forth in claim 9 wherein said bioactive material is a therapeutic agent.

CLPR:

11. A device as set forth in claim 9 wherein said bioactive material is a diagnostic agent.

CLPR:

12. A device as set forth in claim 9 wherein said device is a vascular graft having said primary lumen disposed to form a blood flow pathway.

CLPR:

13. (Amended) A device as set forth in claim 9 wherein said device is an organ graft having said primary lumen disposed to form an organ to organ fluid flow pathway.

CLPR:

14. A device as set forth in claim 9 wherein said body consists of polytetrafluoroethylene.

CLPR:

15. The device of claim 14 wherein said polytetrafluoroethylene is selected from the group consisting of, expanded polytetrafluoroethylene, stretched polytetrafluoroethylene, and stretched and expanded polytetrafluoroethylene.

CLPR:

16. A device as set forth in claim 14 wherein said bioactive material is a therapeutic agent.

CLPR:

17. A device as set forth in claim 14 wherein said bioactive material is a diagnostic agent.

CLPR:

18. The device of claim 9 wherein said body consists of a material including copolymers.

CLPR:

19. An implantable prosthetic device for delivering a bioactive material into a blood vessel of a patient, the device comprising a single tubular body extruded as a continuous wall, said wall consisting of a polytetrafluoroethylene and formed as a continuous extrusion having at least two lumina formed therein including a primary lumen adapted for attachment to a blood vessel of the patient and a secondary lumen,

CLPR:

20. The device of claim 19 wherein said wall is a polytetrafluoroethylene is selected from the group consisting of expanded polytetrafluoroethylene, stretched polytetrafluoroethylene, and stretched and expanded polytetrafluoroethylene.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw=Desc	Image
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 2. Document ID: US 5374395 A

L5: Entry 2 of 4

File: USPT

Dec 20, 1994

DOCUMENT-IDENTIFIER: US 5374395 A

TITLE: Diagnostics instrument

BSPR:

Antibody detection methods take advantage of antibodies. An antibody is a protein molecule that is produced in the normal immune system as immune response to foreign (non-self) material. The foreign material is called an antigen. Producing an immune response is called antigenic. Many microorganisms are antigenic to the human body, so antibodies are produced when exposure to the microorganism has occurred.

BSPR:

The original antibody detection method involves the detection and often quantification of the antibody in the blood of the patient. The principle of the method is based on the very specific binding of the antibody to the antigen. If both the antigen and antibody are present, they will form a chemical bond analogous to a lock and key. In the simplest of these methods, the blood sample, potentially containing the antibody, is mixed with the antigen that has a radioactive detector built into its structure. If the antibody and antigen are both present, they will bond producing a radioactive signal indicating a positive reaction. If the antibody is not present in the sample, the antigen will be washed away and the reaction will not produce a radioactive signal. Due to the potential hazards of dealing with radioactive materials, the original methods have largely been replaced by enzymatic detectors that show a color reaction when positive. Other methods, based on the antibody-antigen bond have been developed that combine multiple antibodies and antigen systems to increase specificity. Since they are proteins, antibodies can also be detected by common protein detection methods, such as electrophoresis.

BSPR:

Spaced apart from the processing assembly is a test pack carrier assembly to carry the test packs. The test pack carrier assembly can be in the form of a turntable, carousel, belt conveyor, or other carrying mechanism or holding device. A motor or other dynamic moving means are provided to move the test pack carrier assembly and the optical detection assembly relative to each other so that the test packs are sensed by the optical detection assembly at timed intervals. In the illustrative embodiment, both the test pack carrier assembly and the optical detection assembly are moveable and driven by motors.

DEPR:

The side panel 106 (FIG. 1) of the automated diagnostics instrument provides power to the entire instrument and allows the instrument to communicate with other devices. The side panel has: a disk drive, four interface ports, a parallel interface, a serial interface, a video port, connector socket, a power switch, and a fuse. The disk drive copies information to diskettes. Four interface ports can connect components to the automated diagnostics instrument. A parallel interface can be provided for an optional printer. A serial interface can be provided to connect to another computer. A video port can be provided for a monitor 116 with a computer screen 118. A round connector socket can be provided for a computer keyboard 120. A power socket connects to the three-pronged power cord. An ON/OFF power switch turns the automated diagnostics instrument power on and off. A fuse protects the instrument from power surges.

DEPR:

The electronics module 124 of the automated diagnostics instrument can include two IBM compatible PC motherboards in a master-slave configuration in order to provide the microprocessing power in the automated diagnostics instrument. The master system can comprise a 33 Mhz 386 motherboard with a hard disk, floppy disk drive and VGA graphics. The slave motherboard can be a 33 Mhz 386 with VGA graphics. An interface card can contain an EPROM with slave software on it, and provides a bus to the main system motherboard. Four main electronics boards plug into the system motherboard which then distributes signals and power to the diagnostics instrument. The four main boards are: (1) digital board, which

decodes the servo motor encoders and reads the opto switches; (2) servo board, which provides power drivers for the motors and heaters; (3) a pneumatics board, which provides drivers for the pneumatics valves and pump and regulates the heater mat sensors; and (4) reader electronics. The main function of these four boards is to provide sensors and drivers which form a number of closed loop servo systems. Additional boards can include a programmable constant current driver to power the sealers and reader photodiode preamplifier. The bar code readers communicate with the slave via an interface. The electronic module 124 (FIG. 9) comprising the computers, keyboard and display screen are wired to and receive signals from the bar code reader and read head. The computers are also connected to the processing station and assembly to control the sequence of operations of the processing station and assembly in accordance with the necessary sequence of steps to conduct the desired tests of the samples in the test packs in the processing station.

DEPR:

The load door 110 (FIG. 2) comprises an assembly which includes: a light emitting diode (LED) status indicator and label 128, a door lock 130, a proximity actuation switch 132, a load door strike plate 134, and a retention magnet 136. The door lock 130 secures the load door 110 after the test pack has been loaded therein for controlled handling and uninterrupted protocols. The LED indicator 128 shows the status of the diagnostics instrument 100. The retention magnet 136 is provided to assist and facilitate locking of the load door. The actuation proximity switch 132 disables the load tram motor drive when the load door is open. The load door is designed to be opened using one hand in position while the other holds the test pack. The load door can only be opened when the door lock 130 is off and the LED indicator 128 for load is lit up. The test pack is loaded into the load station area by placing the bottom edge of the test pack into the lower load shuttle of the load tram and pushing down on the lower spring plate. The top edge of the test pack is then pushed into the top load shuttle. Once loaded, the load door is closed and the magnet and lock are activated before the next operation. Unloading of the processed, tested test pack from the load door is the reverse of loading.

DEPR:

As shown in FIG. 10, the load tram 300 has: an upper load tram assembly 324, a load tram support 326, a load tram motor gearbox and encoder 328, a load spring 330, a lower load tram assembly 332, a thermal door assembly 334, a drive shaft 336 and a rotary cylinder 338. The twin drive belts 308 and 310 of the upper and lower load tram assemblies 324 and 326 are driven by a single motor gearbox 328. An encoder on the gearbox motor assists in obtaining accurate placement of the test pack on the carousel. The drive belts 308 and 310 can be steel/kevlar reinforced to avoid belt stretch and reduce backlash. Tensioner plates 340 and 341 (FIGS. 10, 12 and 13) at each end of the upper and lower tram assemblies can be provided to adjust tile tension of the drive belts 308 and 310. Couplings 344 (FIG. 11) are provided to allow easy drive connection between the shaft 336 of the upper and lower load tram assemblies. A lower drive clamp 348 (FIG. 11) is provided to attach the motor gearbox and encoder to the drive system. Air driven thermal door assemblies 334 (FIG. 10) provide a thermal seal for the load tram. An end of limit opto device 346 (FIG. 13) on tile lower rail assembly is provided for set up calibration on start up of the diagnostics instrument.

DEPR:

As shown in FIG. 14, the processing (processor) tram 302 has: an upper processor tram assembly 350, tie bars 352 and 353, a processing tram drive shaft 354, a lower processor tram assembly 356, a processing tram motor gearbox and encoder 358, and test pack location springs 360 and 361. The twin drive belts 308 and 310 of the upper and lower processing tram assemblies are driven by a single motor gearbox 358. An encoder on the motor 358 helps obtain accurate positioning of the test packs. Couplings 362 (FIG. 17) are provided to allow easier drive connection between the shaft 354 of the upper and lower assemblies. The drive belts 308 and 310 of the processing tram can be steel/kevlar reinforced to avoid belt stretch and reduce backlash. Processing tram tensioner plates 364 and 366 (FIGS. 14-16) at each end of the upper and lower processing tram assemblies can be provided to adjust the tension on the drive belts 308 and 310. An end-of-limit opto device 368 (FIG. 16) on the lower rail processing tram assembly is provided for set-up calibration on start up of the diagnostics instrument. A lower drive clamp 370 (FIG. 17) is provided to attach the motor gearbox encoder 358 to the drive system of the processor tram.

DEPR:

The carousel is driven by a servo-controlled 12 V DC motor driven via a carousel gear 414 (FIG. 37) and pinion drive spur gear. The locking pin 115 can be made of stainless steel. The locking pin prevents rotation of the carousel during loading and unloading of the test packs by the load and processor trams, as well as during the read cycles of the read head mechanism. The locking pin is reciprocally driven by a double-acting pneumatic cylinder 418 mounted to a bracket 420. Read switches can control and monitor the status of the locking pin. The locking pin itself has a tapered end that is designed to locate into a slot 420 in the carousel gear 414 rather than passing through it, which helps ensure accurate positive engagement. The locking pin can slide within a bearing 422.

DEPR:

The clamp plate assembly 604 (FIGS. 25 and 26) has a clamp plate 632 which provides the supporting mechanism of the processing station. The clamp plate holds the test pack while it is in the processing station. The clamp plate surface conforms exactly to the back of the test pack so that all parts of the test pack are fully supported when the saddle applies pressure to the test pack during processing. The clamp plate pushes a newly delivered test pack against the saddle. The clamp plate retracts at the end of the pack's processing station session, allowing the processing tram to return the test pack to the carousel. Four square cut-out areas 640 in the clamp plate allow magnets 606 to advance and touch four areas 214 of the back plate 204 of the test pack 200 to pull magnetic beads out of solution. Each magnet is moved by its own pneumatic device.

DEPR:

The primary function of the clamp (clamping) plate assembly is to support and clamp the test pack in the correct position while it is being processed by the processor assembly. The clamp plate assembly also provides the reaction force necessary to maintain equilibrium during chemistry processing of the test pack. The clamp plate moves along a linear track 638 (FIG. 261, and is powered by pneumatics at the top and bottom of the clamp plate. The linear guide takes the weight off the whole clamp plate assembly and maintains an accurate linear displacement upon actuation. The clamp plate assembly is driven by two double-acting pneumatic cylinders 642 which are actuated by read switches. The pneumatic cylinders are coupled to the clamp plate with rod end bushings and pins to ensure that the correct line of force is maintained.

DEPR:

The magnet assembly is coupled to the double-acting pneumatic cylinder which provides the required reciprocating linear movement of the magnet so as to ensure that the magnet is engaged to the test pack when required and retracted away when not required. The pneumatic cylinder piston movement and magnet movement is actuated and controlled by reed switches mounted to the pneumatic cylinder. Coupling of the magnet assembly to the pneumatic cylinder is accomplished by a pin push fitted into the magnet yoke after passing through a piece of plastic tubing 651 (FIG. 34) within the hole of a separate connecting bar. The coupling arrangement allows a flexible degree of freedom in each axis to allow the magnet assembly to have a degree of free float to prevent clogging and sticking when being driven by the rigidly fixed double acting pneumatic cylinder through a rigidly fixed guide block.

DEPR:

The function of the wastegate assembly is to provide a temporary mechanical sealing gate to each of four waste areas on the test packs (TSP). This is achieved by a single vane rotary air actuator providing the drive force to an eccentric stainless steel cam 658 (FIG. 32) which in turn activates four independent gates. The cam 658 has multiple cam sections 659 which provide linear displacement of the wastegate from the given 180.degree. rotation provided by the air actuator. Acetal cam followers 660 provide a link between the cam 658 and a travelling wastegate wall or floor 662. The wastegate wall or floor 662 is in contact with the cam 658 to provide a positive return device. Pins 664 pass through the cam followers 660 and spring-loaded wastegate feet 666. The springs in the wastegate feet provide a preload which is transmitted to the pouch surfaces of the test pack upon contact to ensure the correct sealing force and pressure is applied during sealing. Each of the individual wastegate feet are guided and positioned by a single guide block 670 containing acetal bearings to free and smooth running. Wastegate sealing inserts 672 are placed on the end of

each of the wastegate feet 666 to contact and seal the waste pouches in the test packs. The wastegate inserts 672 have a self-levelling section 673 (FIG. 33), a locating fixing section 674 and a sharp edge 675 comprising a sealing member that provides the required sealing characteristics of the test pack pouch.

DEPR:

The processor saddle 610 (FIG. 18) is a compact mechanism and assembly housed and maneuvered vertically within the processor. Its purpose is to manipulate the reagent fluids and test sample within the test pack in order to carry out a specific assay. The test pack manipulations required are: (a) blister making; (b) blister expression; (c) blister sealing after expression; (d) rolling waste fluid into waste blister; (e) reaction area fixing; (f) rolling target fluid into next reaction area; (g) sealing reaction area after use; and, (h) rolling amplification of the tested sample (cocktail) into the read cell. The saddle 610 uses six saddle actuators to accomplish this set of manipulations. The saddle actuators are driven by two servo-motors via a set of interleaved cams 684 mounted on two cam shafts. The cam shafts include a roller cam shaft 687 (FIG. 41) and an expression cam shaft 688, which have a set of position or states, e.g. dwell positions. The positions/states of the roller camshaft 687 include: (1) high pressure roller and reaction area seal [RASEAL]; (2) high pressure roller; (3) both rollers; (4) low pressure roller; (5) off; and (6) side sealers [SSEAL]. The position/states of the expression camshaft 688 include: (1) both shoes; (2) back shoe; (3) off; and, (4) front shoe. The position/states of the cam shafts are positioned at 60.degree. intervals. The roller camshaft 687 is physically prevented from entering the interstate condition between the side sealer 626 and the high pressure reaction sealer 628 by the complimentary shapes of the sealer cams. The diagnostics instrument safely resets the saddle cams 684 by sensing the calibration opto device and resetting in the opposite direction if the opto device is blocked.

DEPR:

The saddle can be electrically connected to the processor frame by a conduit chain through which cables 138 (FIG. 18), ribbon cables and extra-flexible sealer cables run. These can be led to the distribution board where the motors, encoders and opto-devices are joined. The sealers can also be connected by flexible cables through an enclosed protective conduit to the distribution board.

DEPR:

The pneumatics schematic flow diagram of FIG. 27 diagrammatically illustrates the pneumatic circuit 700 of the diagnostics instrument. The pneumatic circuit 700 controls and supplies air to all assemblies, components and modules of the diagnostics instrument that contain some form of pneumatic actuation. The pneumatic circuit 700 has a pneumatic vessel or tank comprising an air reservoir 702. Connected to the reservoir via a non-return valve 704 is a pump (compressor) 706 having a silencer 708. Also, serially connected to the reservoir are: a pressure regulator 710, electro-pneumatic pressure switches 712 and 714, pressure gauges (switches) 716 and 718 and a clump valve 720. A ten-way manifold 722 having solenoid direct-acting pneumatic valves 724-731 is pneumatically connected to pneumatic cylinders 732-740 and to the pressure regulator 710. The ten-way manifold 722 includes: a locking pin valve 724, a thermal door valve 725, a wastegate valve 726, a clamp plate valve 727, and magnet (magnetic) valves 728-731 for the beads. The locking pin valve 724 is connected to a carousel locking pin cylinder 732 via a six-way connector 742. The thermal door valve 725 is connected to a load tram thermal door cylinder 733 via a six-way connector 742. The wastegate valve 726 is connected to a wastegate cylinder 734 via a 12-way connector 744. The clamp plate valve 727 is connected to the top and bottom clamp plate cylinders 735 and 736. The magnet valves 728-731 are connected to the magnet (magnetic) cylinders 737-740.

DEPR:

In the pneumatic circuit, the pump 706 can run until 90 seconds after the reservoir's upstream pressure switch (pressure gauge) detects 4 bar pressure. The pump restarts when the pressure switch (pressure gauge) 716 detects that the pressure has dropped below 4 bar, sending a signal to the central processing unit. A non-return valve 704 stops any leak through the pump and provides an easier start for the pump by alleviating back pressure which can otherwise cause pumps to stall. The air reservoir 702 can then be regulated to 3.75 bar and is monitored by a second pressure switch (pressure gauge) 718 which indicates the downstream pressure. A bank (manifold) 722 of solenoid-operated direct-acting

valves 724-731 are used to govern the air flow to each assembly and pneumatically operated components, making sure that they are actuated at the correct time via signals from the central processing unit. The pneumatic circuit has silencers 708 and 746-748 to reduce noise levels for exhausting air and a dump valve 720 which is turned on and off by an electrical switch.

DEPR:

Sample processing tubes can be used to hold the sample before it is injected into the test pack. The processing tube can be designed to work with a sample transfer device and can be optimized for any special pre-processing that might be required for the sample. Sample transfer devices can be used to allow the operator to inject the correct amount of the sample directly from the sample processing tube into the test pack. One end attaches to the sample processing tube and the other end screws into the test pack. A filter can be used in the sample transfer device to ensure that only a clear sample is delivered into the test pack. A loading nest can be provided to support the test pack while the operator injects a sample into the pack. The loading nest resists movement while the operator attaches the sample transfer device to the test pack.

DEPR:

The sample port 220 (FIG. 23) on the back 243 of the test pack is where the operator injects the patient sample into the test pack. The sample port can comprise a conical socket 262 with a Luer-type lock fitting 264 which exactly fits and locks to a sample transfer device, ensuring injection of the correct volume of sample and eliminating the chance of leakage during injection. The sample inlet cap 268 can comprise a conical Luer-type plug that covers the sample port. The sample inlet cap can be affixed to the sample port during manufacture, and is preferably only removed to insert the patient sample. Then, the cap should be replaced.

Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC	Draw Desc	Image
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☐ 3. Document ID: US 5071248 A

L5: Entry 3 of 4

File: USPT

Dec 10, 1991

DOCUMENT-IDENTIFIER: US 5071248 A

TITLE: Optical sensor for selective detection of substances and/or for the detection of refractive index changes in gaseous, liquid, solid and porous samples

BSPR:

The present invention refers to an optical sensor according to the main patent claim. A well-known device for measuring refractive index changes in liquids, solids and porous samples is the refractometer which determines the angle of total internal reflexion between two media where the reference medium is a high index prism of known refractive index. A well-known device for the detection of chemisorbate layers and of chemically bound layers on surfaces is the ellipsometer analysing the state of polarisation of the light being reflected at the chemisorbate layer (cf. R. Azzam et al., Physics in Medicine and Biology 22 (1977) 422-430; P. A. Cuyper et al., Analytical Biochemistry 84 (1978), 56-67). These devices are voluminous and the required sample volume is rather big what can be a great disadvantage in case of expensive samples. Furthermore the measurement accuracy of an ellipsometer is limited since the cell containing the liquid can influence the state of polarisation of the light. Another well-known instrument for the detection of adsorbed antigens, antibodies and haptens is the refractometer described in EP 0073980. A relatively new method for the detection of adsorbate layers is based on the excitation of surface plasmons at metal layer interfaces with or without using a diffraction grating (cf. B. Liedberg et al., Sensors and Actuators 4 (1983), 299 and EP 0112721). Thin metal films are not very stable and show ageing effects in their optical properties, what may be causing problems in practical applications. When the coupling between an analyte and the chemoresponsive layer is accompanied by a colour change, spectral

photometry is another method for detecting (bio)chemical substances. E. E. Hardy et al describes a spectral photometer (see Nature 257 (1975), 666-667) where light is guided in an optical waveguide. The waveguide is a quartz rod of macroscopic dimensions (1 mm in diameter). This waveguide is a typical multimode waveguide. The measuring method is based on the fact that the light transmission of the quartz rod covered by a chemoresponsive layer is change when the (bio)chemical substance to be assayed adsorbs to the quartz rod.

BSPR:

The methods mostly used for the immunological determination of antibodies, antigens and haptens and for the determination of concentrations of metabolites such as glucose are based on the use of markers such as radioisotopes, enzymes or fluorescent tracers (EP 0103426, U.S. Pat. No. 4,344,438), which are chemically bound to a counter ligand, that is, to a complementary biomolecule. Sometimes, however, labeling leads to a perturbation of the binding behaviour of the corresponding biomolecule what means a decrease of the binding affinity.

DRPR:

FIG. 2 is in accordance with the invention a schematic view of a measuring device operating as an input grating coupler.

DRPR:

FIG. 3 is in accordance with the invention a schematic view of a measuring device operating as an output grating coupler.

DRPR:

FIG. 4 is in accordance with the invention a schematic view of a measuring device operating as a Bragg reflector.

DRPR:

FIG. 7 is in accordance with the invention a schematic view of a device for indirect measurement of the intensity of a guided lightwave where the scattered light produced by the guided wave is collected by a fiber and sent to a detector.

DRPR:

FIG. 8 is in accordance with the invention a schematic view of a device for indirect measurement of the intensity of a guided lightwave where the intensity of one or several non-incoupled diffraction orders is measured.

DEPR:

Furthermore this principle of selectivity of the optical sensor can be used in immunology to identify antigen-antibody complexes. As an example the additional layer 5 consists of molecules of a certain antigen. Then coupling between antigen and antibody can only take place when the corresponding antibody is contained in the sample 3. In this example the chemisorbed layer 6 consists of antibody molecules. The degree of coverage of the chemisorbed layer 6 depends on the antibody concentration in the sample 3 as well as on the time of incubation. Thus the present optical sensor can be applied to the determination of antibody concentrations by measuring the maximum degree of coverage or the stationary degree of coverage being established after a certain time.

DEPR:

The organisation and regulation of all biological systems is guaranteed by the selective recognition of biomolecules via the lock-and-key principle. Therefore this principle can also be applied to biosensorics. Besides antigens and antibodies also other pairs of biomolecules show complementary behaviour such as haptens and antibodies, enzymes and enzyme inhibitors, hormones or neurotransmitters and receptors, or complementary nucleic acids. All these kinds of complementarity can be used as selectivity principle for the optical sensor where one of the two complementary biomolecules is immobilized on the waveguiding film 1 and thus forms the additional layer 5. The other biomolecule forms the layer 6.

DEPR:

The lock-and-key principle can also be used in a more elaborated way. Well-known is the so-called sandwich method where the lock-and-key principle is carried out repeatedly (example: antibody-antigen-antibody complex formation). Well-known is also the so-called competition method where two different species of biomolecules

mostly of different molecular weight compete for the same binding sites at the receptor molecules (i.e. at the additional layer 5). When the concentration of one species of molecules contained in the sample 3 is increased the other species of molecules is partially expelled from the binding sites of the receptor molecules (EP 0073980). This desorption leads to a detectable change in thickness of layer 6. Thus the thickness change is a measure for the concentration of the species of molecules to be detected. A further possibility of concentration measurement lies in the observation of the dynamical behaviour of the adsorption or binding process. The thickness change of layer 6 as function of time or the velocity of growth of layer 6, respectively, determine the concentration of the specific substance to be detected (cf. G. Traexler, Medizintechnik 99 (1979), 79-84, J. C. Sternberg, Clin. Chem. 1456 (1977).

DEPR:

FIG. 3 shows in accordance with the invention the measuring device used as an output grating coupler. Waveguide 1/2, diffraction grating 4 and selectively chemisorbing additional layer 5 are described in the context of FIG. 1. When a guided mode 8 falls on the diffraction grating 4 the laser light is partially or completely coupled out. The outcoupled laser beam 9 leaves the waveguide 1/2 for a constant wavelength under a certain angle W2 which is determined by the effective index. Excitation of the guided mode 8 is not shown in FIG. 3. For example, the guided mode can be excited by endfire coupling, prism coupling, grating coupling etc. (cf. T. Tamir, Integrated Optics, Chap. 3). A change of the effective index induced by the sample 3 in the grating region leads to a change of the outcoupling angle W2. This change in angle can for example be measured by a photodiode array or a position dependent photodetector D2. For small angle changes of the outcoupled laser beam 9 it is also possible to measure the change of intensity of the outcoupled laser beam 9 incident onto a detector D2 having a smaller detection area than the beam diameter area since the outcoupled laser beam 9 moves across the detector D2 during the measuring procedure. From the change of angle or the change of intensity, respectively, the change of effective index is determined.

DEPR:

For simultaneous excitation of two different modes of same wavelength by an input grating coupler (see FIG. 2) two laser beams have to be simultaneously incident onto the diffraction grating 4 at two different angles of incidence. This can be accomplished even with one laser by using an appropriate beam splitting device.

ORPL:

Tiefenthaler et al., "Integrated Optical Switches and Gas Sensors", Optics Letters, vol. 10, No. 4 (Apr. 1984), pp. 137-139.

ORPL:

Sutherland et al., "Optical Detection of Antibody-Antigen Reactions at a Glass-Liquid Interface", Clinical Chemistry, vol. 30, No. 9 (1984), pp. 1533-1538.

Full	Title	Citation	Front	Revers	Classification	Date	Reference	Claims	KWC	Draw	Desc	Image
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☐ 4. Document ID: US 4815843 A

L5: Entry 4 of 4

File: USPT

Mar 28, 1989

DOCUMENT-IDENTIFIER: US 4815843 A

TITLE: Optical sensor for selective detection of substances and/or for the detection of refractive index changes in gaseous, liquid, solid and porous samples

BSPR:

The present invention refers to an optical sensor according to the main patent claim. A well-known device for measuring refractive index changes in liquid, solids and porous samples is the refractometer which determines the angle of

total internal reflexion between two media where the reference medium is a high index prism of known refractive index. A well-known device for the detection of chemisorbate layers and of chemically bound layers on surfaces in the ellipsometer analysing the state of polarisation of the light being reflected at the chemisorbate layer (cf. R. Azzam et al., Physics in Medicine and Biology 22 (1977) 422-430; P. A. Cuyppers et al., Analytical Biochemistry 84 (1978), 56-67). These devices are voluminous and the required sample volume is rather big what can be a great disadvantage in case of expensive samples. Furthermore the measurement accuracy of an ellipsometer is limited since the cell containing the liquid can influence the state of polarisation of the light. Another well-known instrument for the detection of adsorbed antigens, antibodies and haptens is the refractometer described in EP 0073980. A relatively new method for the detection of adsorbate layers is based on the excitation of surface plasmons at metal layer interfaces with or without using a diffraction grating (cf. B. Liedberg et al., Sensors and Actuators 4 (1983), 299 and EP 0112721). Thin metal films are not very stable and show ageing effects in their optical properties, what may be causing problems in practical applications.

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DRPR:

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DRPR:

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DRPR:

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DRPR:

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DEPR:

Furthermore this principle of selectivity of the optical sensor can be used in immunology to identify antigen-antibody complexes. As an example the additional layer 5 consists of molecules of a certain antigen. Then coupling between antigen and antibody can only take place when the corresponding antibody is contained in the sample 3. In this example the chemisorbed layer 6 consists of antibody molecules. The degree of coverage of the chemisorbed layer 6 depends on the antibody concentration in the sample 3 as well as on the time of incubation. Thus the present optical sensor can be applied to the determination of antibody concentrations by measuring the maximum degree of coverage or the stationary degree of coverage being established after a certain time.

DEPR:

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where one of the two complementary biomolecules is immobilized on the waveguiding film 1 and thus forms the additional layer 5. The other biomolecule forms the layer 6.

DEPR:

The lock-and-key principle can also be used in a more elaborated way. Well-known is the so-called sandwich method where the lock-and-key principle is carried out repeatedly (example: antibody-antigen-antibody complex formation). Well-known is also the so-called competition method where two different species of biomolecules mostly of different molecular weight compete for the same binding sites at the receptor molecules (i.e. at the additional layer 5). When the concentration of one species of molecules contained in the sample 3 is increased the other species of molecules is partially expelled from the binding sites of the receptor molecules (EP 0073980). This desorption leads to a detectable change in thickness of layer 6. Thus the thickness change is a measure for the concentration of the species of molecules to be detected. A further possibility of concentration measurement lies in the observation of the dynamical behaviour of the adsorption or binding process. The thickness change of layer 6 as function of time or the velocity of growth of layer 6, respectively, determine the concentration of the specific substance to be detected (cf. G. Traexler, Medizintechnik 99 (1979), 79-84, J. C. Sternberg, Clin. Chem. 1456 (1977)).

DEPR:

FIG. 3 shows in accordance with the invention the measuring device used as an output grating coupler. Waveguide 1/2, diffraction grating 4 and selectively chemisorbing additional layer 5 are described in the context of FIG. 1. When a guided mode 8 falls on the diffraction grating 4 the laser light is partially or completely coupled out. The outcoupled laser beam 9 leaves the waveguide 1/2 for a constant wavelength under a certain angle W_2 which is determined by the effective index. Excitation of the guided mode 8 is not shown in FIG. 3. For example, the guided mode can be excited by endfire coupling, prism coupling, grating coupling etc. (cf. T. Tamir, Integrated Optics, Chap. 3). A change of the effective index induced by the sample 3 in the grating region leads to a change of the outcoupling angle W_2 . This change in angle can for example be measured by a photodiode array or a position dependent photodetector D2. For small angle changes of the outcoupled laser beam 9 it is also possible to measure the change of intensity of the outcoupled laser beam 9 incident onto a detector D2 having a smaller detection area than the beam diameter area since the outcoupled laser beam 9 moves across the detector D2 during the measuring procedure. From the change of angle or the change of intensity, respectively, the change of effective index is determined.

DEPR:

For simultaneous excitation of two different modes of same wavelength by an input grating coupler (see FIG. 2) two laser beams have to be simultaneously incident onto the diffraction grating 4 at two different angles of incidence. This can be accomplished even with one laser by using a appropriate beam splitting device.

CLPR:

14. An optical sensor according to claim 13, wherein the chemo-responsive layer comprises antibodies for an antigen which is to be assayed.

CLPR:

21. An optical sensor according to claim 20, wherein the chemo-responsive layer comprises antibodies for an antigen which is to be assayed.

ORPL:

Tiefenthaler et al. "Integrated optical switches and gas sensors", Optics Letters vol 10, No. 4 (Apr. 1984) pp. 137-139.

ORPL:

Sutherland et al "Optical Detection of Antibody-Antigen Reactions at a Glass-Liquid Interface", Clinical Chemistry, vol 30, No. 9 (1984) pp. 1533-1538.

Full	Title	Cratn	Front	Review	Classification	Date	Reference	Claims	KMC	Draw Desc	Image
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